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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/652,799	08/29/2003	Barry Eisenstein	50150/005003	2013

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
FUBARA, BLESSING M	
ART UNIT	**PAPER NUMBER**
1618	

DATE MAILED: 10/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/652,799	EISENSTEIN, BARRY	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/01/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of request for reconsideration and remarks, exhibits A and B, and declaration under 37 CFE 1.132, all filed 07/11/05. Receipt is also acknowledged for IDS filed 09/01/05.

Claim Rejections - 35 USC § 112

1. Claims 1-76 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a subject having an infection of *Clostridium difficile* or inhibiting infection of clostridium in a subject, does not reasonably provide enablement for preventing infection of *Clostridium difficile* in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues that the specification provides enablement for both the treatment and preventive methods and several section of the instant specification is quoted to support the preventing of infection. For example, rifalazil is discussed as being given once, twice, three or four times daily and that at page 5, lines 19-29, an effective amount of rifalazil is defined. Applicant refers to Exhibit A as evidence or support for preventing *C. difficile* infection and *C. difficile* associated diarrhea.

2. Applicant's arguments filed 07/11/05 have been fully considered but they are not persuasive.

The rejection was scope of enablement because the preventing or prevention of the infection is not enabled. For prevention, the condition is to be kept from happening and the data applicant alludes to do not keep the infection from happening. That is to predict that a condition would happen before it happens and by administering such a composition would stop the infection

from infecting the population that was administered the formulation and also that population that was not administered the composition would come down with the infection every time and all the time. The standard for preventing/prevention is high and the data presented deals with treating the infection. A medication administered after indication of infection detected is not preventing but treating the infection related to the bacterial attack.

The scope of protection sought by the claims is prevention/preventing infection of *Clostridium difficile* and the scope of enablement provided to one skilled in the art by applicant's disclosure is determination of minimum inhibitory concentration of rifalazil concentration of *Clostridium difficile* and treatment/treating *Clostridium difficile* associated disease. Specifically, the treatment regimen in Example 1 monitors the survival, weight variations, identification of *Clostridium difficile* toxins in cecal content and histological damage to the ceca after oral gavage of *Clostridium difficile* and administration of rifalazil or rifalazil in combination with a second drug compound. An optimal dosage is then determined. The Anton work concludes treatment and not prevention. Thus, the scope of enablement provided by applicant's disclosure is not commensurate with the protection sought by the claims. Secondly, one skilled in the art is not enabled by the disclosure to make and use the entire scope of the claimed prevention/preventing without undue experimentation since no guidance is provided on how the preventing of an infection of clostridium difficile in a subject is given. Guidance is only provided for a) how to determine optimum dosage of rifalazil or rifalazil in combination with a second drug compound, and b) how to determine the minimum inhibitory concentration of rifalazil for clostridium difficile. The standard for prevention/preventing is high and the high standards require that guidance be provided on how the infection of *Clostridium difficile* is prevented. However, no guidance is provided and there is no experimental data showing prevention/preventing. Exhibit A

does not show data on preventing, the standard for *keeping from happening.* It is suggested that ---treatment--- or ---treating--- be used.

Claim rejections- 35 USC 101/Printed Matter Rejection

Claims 54-75 remain rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Applicant's argument that the office mischaracterized claims 54-75 as a "mere arrangement of printed matter" is not persuasive. It is the instruction that is a mere arrangement of printed matter and not the pharmaceutical. In the case of *In re Miller* cited by applicant, it is respectfully noted that the Miller case has to do with indicia on a measuring tool and it is thus as rightfully pointed out by applicant, in combination with a structural element just as the indicia on a capsule or tablet. However, in this case applicants are claiming instructions for administering the drug and that instruction is arranged on a paper or printed on a paper. The instruction does not appear to be written on the rifalazil.

Claim Rejections - 35 USC § 102

3. Claims 1-11, 13-18, 20-27, 29-45, 48-50, 54-65, 67-73 remain rejected under 35 U.S.C. 102(e) as being anticipated by Michaelis et al. (US 2004,113,4021).

Applicant is of the opinion that the rejection is in error because the instant application claims priority to US 60/406,873 filed Aug. 29, 2002 and to US 60/444,570 filed Feb. 03, 2003 while the Michaelis reference claims priority to US 60/385,532 filed June 03, 2002, and to US 60/406,873 filed Aug. 29, 2002, and to us 60/412,958 filed Sept. 23, 2003. Here the relevant dates are Aug. 29, 2002 for the instant application and June 03, 2003 for the Michaelis reference. Since these dates are valid for the application and the published application, it is respectfully noted that June comes before August and this date is good as a 102(e) date since June 03, 2002 comes

before August 29, 2002. Therefore, the rejection is not in error. Secondly, applicant states that there is no mention of *clostridium difficile* in the document 60/385,532. However, cursory review of the provisional application shows in claims 9 and 11, page 4, line 23 and page 5, line 9 that other clostridium spp. can be used and *closrtridium perfringens* and *clostridium difficile* are *spp.* of *clostridium.* Other *clostridium spp.* encompasses *clostridium difficile.* (*Clostridium spp.*, including *Clostridium difficile, Clostridium tetani, Clostridium botulinum, Clostridium perfringens* are known in the art).

Claim Rejections - 35 USC § 103

4. Claims 1-11 and 54-58 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberland et al. (US 6,114,310) in combination with Rose et al. (US 6,316,433).

Applicant agues that Chamberland does not disclose the use of rifamycin or any antimicrobial agent alone for treatment of any microbial infection, and that rifamycins are not called out specifically for the treatment of C. difficile or any other specific microbial infection; that it is the efflux pump inhibitors and not antibiotics that Chamberland touts as effective antibacterial compounds; that because Chamberland lists 141 agents, the selection of rifamycin is one in 141.

5. Applicant's arguments filed 07/11/05 have been fully considered but they are not persuasive.

Chamberland discloses efflux inhibitors in combination with antimicrobial agents and in the process, Chamberland discloses rifamycin as one of the antimicrobial agents that can be used with the efflux pump inhibitors. A list of 141 is not an exhaustive list. Rose is relied upon for a teaching that rifalazil is a known rifamycin. Secondly, in response to applicant's argument regarding selecting from 141 members of a list, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). And the examiner recognizes that combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion can only establish obviousness, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Comprising in the claims is open. In this case, rifalazil is known rifamycin in the art.

6. Claims 13, 34, 35, 37-53, 59 and 73-75 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberland et al. (US 6,114,310) in combination with Rose et al, (US 6,316,433) in further combination with Bostwick et al. (US 5,773,000).

Applicant argues that rifalazil was not previously known for effectively treating *clostridium difficile* and that Chamberland does not disclose use of rifamycin to treat *clostridium difficile;* Rose and Bostwick do not remedy the deficiency.

7. Applicant's arguments filed 07/11/05 have been fully considered but they are not persuasive.

Chamberland (column 16, lines 22-31) uses antimicrobial agent and efflux pump inhibitor. Rose is relied upon for a teaching that rifalazil is a known rifamycin and thus contributes to the disclosure of Chamberland that rifamycin, (an example of which is rifalazil according to Rose) is used in combination with efflux pump inhibitors to treat microbial infections. Bostwick (abstract; column 2, line 63 to column 3, line 11) discloses treating *clostridium difficile* associated diseases

with antibodies and with antibodies in combination with antibiotics such as vancomycin bacitracin and metronidazole. Thus Bostwick discloses using combination of antibodies and antibiotics to treat C. *difficile* and does not teach away from the claimed invention. It is also respectfully noted that Bostwick discloses: "because the present antibodies first eliminate the *C. difficile* toxins, it is also advantageous to administer to patients suffering from *C. difficile* associated diseases a combination of the antibodies of the present invention with antibiotics prior known for treating pseudomembranous colitis and/or antibiotic associated diarrhea. Such antibiotics are for example vancomycin, bacitracin and metronidazole. Because of the speedy and quick elimination of the *C. difficile* toxins, the combination of antibody and antibiotic may be synergistic requiring much less antibiotic normally used in treating such diseases with results of decreased 'symptoms development, faster symptomatic relief and lower relapse rate. Recognized doses for administering metronidazole for example is 250 mg four times a day, and oral vancomycin is 125 mg four times a day. Administration of these antibiotics with the antibody of the present invention would result in use of substantially reduced dosage of antibiotics."

8. Claims 12, 14-33, 36 and 60-72 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberland et al. (US 6,114,310) in combination with Rose et al, (US 6,316,433) in further combination with the admission of applicants in the specification.

Applicant maintains that a combination of additional drugs with rilafazil is not known in the art at the time the invention was made and that Chamberland's inclusion of rifamycins in a list of 141 possible antibacterial agents and *C. difficile* as one of 89 possible microbial infections does not amount to a disclosure of rifamycins for the treatment of a *C. difficile* infection.

9. Applicant's arguments filed 07/11/05 have been fully considered but they are not persuasive.

Chamberland discloses treating *C. difficile* infection with a combination of efflux pump inhibitors and antibiotics and rifamycin is one of the general classes of antibiotics disclosed (see also claims 1, 5, 10 and 15). Rose discloses that rifalazil belongs to the general class of rifamycin and rifalazil is used to treat bacterial infections. Thus it would be obvious that a member of the rifamycin class/group of antibiotics would be used to treat *C. difficile*, specifically, in this case, rifalazil, a rifamycin can be used to treat *C. difficile* infection.

Declaration by Dr. Charalabos Pothoulakis:

The declaration is not persuasive because it is not commensurate with the scope of the claims. A statement that "vast majority of the antibacterial agent contribute to *C. difficile* infections by disrupting the normal environment of the colon" without experimental data showing the difference between the claimed invention and combination of Chamberland and Rose is not persuasive and does not address the scope of the claimed invention.

Regarding the Hill reference (US 2002/0025924 A1) cited in the Form PTO 1449, submitted 09/01/05

Examiner has reviewed the reference and found that the reference discloses using its method to treat bacterial infection caused by gram-positive bacteria such as *clostridium difficile* (paragraph 191) with a composition comprising lipopetide and antibacterial agent such as rifalazil (paragraph 195). The comprising language of the claims is open.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 3:30 p.m. (Monday to Friday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BF

Blessing Fubara
Patent Examiner
Tech. Center 1600

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600